# Low Tidal Volume (Lung Protective) Ventilation Literature Review

Low tidal volume (lung-protective) ventilation (LTVV) is associated with decreased acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) progression as well as a shorter length of stay (LOS). The Society for Healthcare Epidemiology of America guidelines highlight the use of low tidal volume strategy, and newer publications in the field accept LTVV as an effective intervention.

### Society for Healthcare Epidemiology of America

*2014 –* *Strategies To Prevent Ventilator-Associated Pneumonia in Acute Care Hospitals: 2014 Update* 1

Suggests that evidence-based interventions designed to shorten the duration of mechanical ventilation may include low tidal volume ventilation among other strategies, such as paired daily spontaneous awakening and breathing trials, intermittent recruitment maneuvers, and early mobility.

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| **Relevant Studies, 1990–2015** | |
| **Study Type and Author** | **Results Details in Annotated Bibliography** |
| Retrospective Cohort Study (Serpa-Neto, 2015)2 | **PRO:** Conducted a retrospective cohort study to determine the relationship between tidal volume and the onset of pulmonary complications in intensive care unit (ICU) patients without acute respiratory distress syndrome (ARDS). The study placed patients into tidal volume groups based on the tertiles of tidal volume size during the first 2 days of ventilation. "Ventilation with low tidal volumes is associated with a lower risk of development of pulmonary complications in patients without acute respiratory distress syndrome." |
| Randomized Controlled Trial (RCT) (Fernandez-Bustamante, 2014)3 | **CON:** Observed the immediate tidal volume-related changes on lung injury biomarkers in patients with healthy lungs and low risk of pulmonary complications. Randomized 28 healthy knee replacement surgery patients prospectively to volume-controlled ventilation with 6 or 10 mL/kg predicted body weight (PBW) and found no significant tidal volume-related changes in the selected lung injury biomarkers of these patients (in the two groups) with healthy lungs after 60 minutes of ventilation. |

| **Relevant Studies, 1990–2015** | |
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| **Study Type and Author** | **Results Details in Annotated Bibliography** |
| Multicenter, Double-Blind, Parallel-Group Trial (Futier, 2013)4 | **PRO:** Randomly assigned 400 adults at risk of pulmonary complications after major abdominal surgery to either nonprotective mechanical ventilation or a strategy of lung-protective ventilation. Fewer patients (5.0%) assigned to lung-protective ventilation required noninvasive ventilation or intubation for acute respiratory failure as compared to 34 (17.0%) patients assigned to nonprotective ventilation. Also, length of stay (LOS) was shorter among patients receiving lung-protective ventilation as compared to the other group receiving nonprotective mechanical ventilation. |
| Prospective Randomized, Open-Label, Clinical Trial  (Severgnini, 2013)5 | **PRO:** Conducted a study to determine the effectiveness of protective mechanical ventilation during open abdominal surgery on a modified Clinical Pulmonary Infection Score (CPIS) (primary outcome) and postoperative pulmonary function. Randomly assigned 58 patients undergoing abdominal surgery lasting more than 2 hours into a standard ventilation strategy (tidal volume of 9 mL/kg ideal body weight and 0 positive end-expiratory pressure [PEEP]) or into a protective ventilation strategy (tidal volume of 7 mL/kg ideal body weight, 10 cm H2O PEEP, and recruitment maneuvers). Protective ventilation strategy (low tidal volume [Vt]) during abdominal surgery improved respiratory function and the modified CPIS, but did not affect LOS. |
| Prospective Chart Review  (Lellouche, 2012)6 | **PRO:** Reviewed 3,434 consecutive adult cardiac surgery patients. Three groups were defined based on the tidal volume delivered on arrival at the ICU: (1) low: <10, (2) traditional: 10­–12, and (3) high: >12 mL/kg PBW. Assessed risk factors for three types of organ failure (prolonged mechanical ventilation, hemodynamic instability, and renal failure) and a prolonged stay in the ICU. Found that tidal volumes of >10 mL/kg are risk factors for organ failure and prolonged ICU stay after cardiac surgery. |
| RCT (Sundar, 2011)7 | **PRO:** Single-center RCT of 149 patients undergoing elective cardiac surgery. Ventilation with 6 versus 10 mL/kg tidal volume was compared. Tidal volume was set at the onset of mechanical ventilation. Median ventilation time was not significantly different. However, a higher proportion of patients in the low tidal volume group were free of ventilation at 6 hours. In addition, fewer patients in the low tidal volume group required reintubation. |
| Prospective RCT (Pinheiro de Oliveira, 2010)8 | **PRO:** The effects of a protective ventilation strategy on systemic and lung production of tumor necrosis factor-alpha and interleukin-8 (5 to 7 mL/kg) were compared with a conventional ventilation strategy (10 to 12 mL/kg), in patients without lung disease. TNF-alpha and IL-8 concentrations were measured in the serum and in the bronchoalveolar lavage (BAL) fluid at admission and after 12 hours of study observation time. There were no differences in TNF-alpha or IL-8 concentrations at 12 hours at first analysis. However, standardization against urea of logarithmic transformed data revealed that TNF-alpha and IL-8 level in BAL fluid were stable in the low Vt group, but increased in the high Vt group (p=0.05 and p=0.03). Use of low tidal volume ventilation (LTVV) may limit pulmonary inflammation in mechanically ventilated patients, even those without lung injury. |
| RCT (Determann, 2010)9 | **PRO:** Randomized, controlled, nonblinded trial comparing mechanical ventilation with tidal volumes of 10 ml versus 6 ml per kg of PBW in 150 critically ill patients without acute lung injury (ALI) at the onset of mechanical ventilation. Primary outcome was cytokine levels in bronchoalveolar lavage fluid and plasma during mechanical ventilation. Secondary outcomes were the development of ALI, duration of mechanical ventilation, and mortality. Data showed that patients treated with conventional tidal volumes had higher levels of cytokines and suggested that these higher cytokine levels may have contributed to higher rates of ALI. |
| Prospective, Multicenter, Observational Study  (Mascia, 2007)10 | **PRO:** Patients with severe brain injury (Glasgow Coma Score <9) were studied for 8 days from admission. The use of high tidal volume and high respiratory rate are independent predictors of acute lung injury. Alternative strategies should be considered to protect the lungs of these patients. |
| Retrospective Cohort Study (Choi, 2006)11 | **PRO:** Cohort study to determine the effects of mechanical ventilation on the alveolar hemostatic balance in patients without preexistent lung injury. Mechanical ventilation with higher tidal volumes and no PEEP promotes procoagulant changes, which are largely prevented by the use of lower tidal volumes and PEEP. |
| Retrospective Cohort Study (Gajic , 2005)12 | **PRO:** Retrospective cohort study of a medical database to identify mechanically ventilated patients who required mechanical ventilation for at least 48 hours without ARDS at the onset of ventilation, to observe progression to ARDS by extracting data on risk factors of ARDS incidence amongst other measures in these patients. Their analyses revealed that the development of ARDS was associated with the initial ventilator settings, such as a high tidal volume, high peak airway pressure, and a high PEEP. |
| RCT  (Schilling, 2005)13 | **PRO:** Discussion of an RCT of 32 patients undergoing open thoracic surgery who were randomized to mechanical ventilation with either tidal volume of 10 mL/kg of 5 mL/kg, during and after surgery. Results indicated mechanical ventilation may induce epithelial damage and a proinflammatory response in the ventilated lung. Reduction of tidal volume during open thoracic surgery may reduce alveolar concentrations of TNF-alpha and of slCAM-1. |
| Retrospective Cohort Study (Gajic, 2004)14 | **PRO:** Tested hypothesis that ALI is associated with known risk factors for ventilator-induced lung injury such as high Vt. Suggested that height and gender (PBW) should be considered when setting up the ventilator and also suggested limiting large tidal volume in patients with ALI as well as in patients at risk for acute lung injury. |
| Randomized Clinical Study (Koner, 2004)15 | **CON:** Performed a randomized clinical study to evaluate the effects of protective and conventional ventilation with or without PEEP, on systemic tumor necrosis factor-alpha, interleukin-6 levels, and pulmonary function during open heart surgery. Based on their findings, the authors could not conclude that protective mechanical ventilation prevents some of the adverse effects of cardiopulmonary bypass on the lung, nor systemic cytokine levels, postoperative pulmonary function, or length of hospitalization. |
| Randomized Clinical Trial (Wrigge, 2004)16 | **CON:** Randomized clinical trial to determine whether mechanical ventilation modifies inflammatory responses during major thoracic or abdominal surgery. Sixty-four patients undergoing elective thoracotomy or laparotomy were assigned to either mechanical ventilation with 12 or 15 mL/kg ideal body weight, respectively, and zero end-expiratory pressure (ZEEP), or 6 mL/kg ideal body weight with PEEP (10 cm H(2)O). Concluded that neither resulted in different pulmonary or systemic levels of measured inflammatory markers. |
| Prospective, Randomized Clinical Trial (Chaney, 2000)17 | **PRO:** Randomized clinical trial to observe if protective ventilation can reduce the damaging postoperative pulmonary effects of cardiopulmonary bypass (which include increases in airway pressure, decreases in lung compliance, and increases in shunt). Protective ventilation decreases pulmonary damage caused by ventilation in normal and abnormal lungs. |
| Randomized Control Clinical Trial (Lee, 1990)18 | **Neither PRO nor CON:** Randomly assigned intubated patients in the surgical intensive care unit (SICU) to Vt=12 mL/kg (n=56) or Vt=6 mL/kg (n=47). Use of LTVV was associated with a statistically significant but clinically irrelevant decrease in oxygenation. The routine use of LTVV appeared safe in selected population of surgical ICU patients. |

| **Reviews and Meta-analyses, 1990–2015** | |
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| **Publication Type and Author** | **Results Details in Annotated Bibliography** |
| Educational Review (Pannu, 2015)19 | Reviewed studies in the medical and surgical literature that addressed "lung-protective ventilation" in patients without ARDS, and focused specifically on the associations with tidal volume, PEEP, and oxygen supplementation settings. Citing that the incidence of ARDS acquired after mechanical ventilation is 6–25%, also concluded that tidal volumes between 6 and 8 mL/kg PBW are safe and typically meet gas exchange targets in the vast majority of patients without ARDS. |
| Systematic Review and Meta-analysis (Sutherasan, 2014)20 | Reviewed 14 RCTs, 1 cross-sectional, and 1 observational study of several different surgical types where the effect of low tidal volume ventilation was compared to that of traditional volume ventilation. Concluded that LTVV with recruitment maneuvers can decrease the development of ARDS, pulmonary infection, and atelectasis, but not mortality in previously noninjured lungs in the perioperative period and the ICU. |
| Educational Review (Futier, 2014)21 | Reviewed clinical evidence regarding the use of mechanical ventilation in patients undergoing abdominal surgery. Concluded that the use of a prophylactic multifaceted strategy of mechanical ventilation, composed of LTVV, moderate PEEP, and repeated recruitment maneuvers, can help improve postoperative outcome after abdominal surgery. |
| Educational Review  (Coppola, 2014)22 | Reviewed current literature on lung-protective ventilation during general anesthesia in patients without ARDS: abdominal, thoracic, and cardiac surgery patients. Concluded that lung-protective ventilation should be considered in the presence of pulmonary disease, prolonged anesthesia, in high-risk patients, or for high-risk surgery. Although lung-protective ventilation may be beneficial for the lung, it may impair the cardiovascular system, reducing venous return and cardiac output and requiring the use of fluids and vasopressors. Thus, the risks and benefits of lung-protective ventilation need to be balanced in each individual patient. |
| Educational Review (Kilickaya, 2013)23 | Summarized the results of observational data, small, randomized studies, and 2 systematic reviews. Suggested that lung-protective ventilation is safe and potentially beneficial in patients without ARDS at the onset of mechanical ventilation. The principles of lung-protective ventilation were included:   * Prevention of volutrauma (tidal volume 4 to 8 mL/kg PBW with plateau pressure <30 cm H2O) * Prevention of atelectasis (PEEP ≥5 cm H2O) * Adequate ventilation * Prevention of hyperoxia   Recommended lung-protective mechanical ventilation as an initial approach to mechanical ventilation in both perioperative and critical care settings. |
| Systematic Review (Fuller, 2013)24 | Performed a systematic literature review of 1,704 studies and included 13 articles (1 randomized controlled trial and 12 observational studies) that studied tidal volume as a predictor variable for ARDS in the finalized analyses. Eight studies showed decreased progression to ARDS when a lower tidal volume strategy was utilized. |
| Educational Review (Lellouche, 2013)25 | Conducted a literature review to examine the use of prophylactic protective ventilation (i.e., LTVV) in patients without ARDS. The authors concluded that current evidence suggests tidal volumes should be 6-8mL/kg PBW in patients at risk of ARDS. |
| Educational Review (Biehl, 2013)26 | Conducted a review to highlight the best ventilator-induced lung injury (VILI) preventive approach in patients with or at risk for ARDS and to critically appraise evidence and expert opinion. Existing evidence favors the practice of low Vt and that normal (low) Vt ventilation is "safe and effective in maintaining gas exchange in patients without ARDS [while in] mechanically ventilated patients at risk of ARDS, exposure to high Vt increases the frequency of ARDS." |
| Review and Meta-analysis (Neto, 2012)27 | **PRO:** Conducted a review and meta-analysis to determine whether use of lower tidal volumes is associated with improved outcomes of patients receiving ventilation who do not have ARDS. Among patients without ARDS, protective ventilation with lower tidal volumes was associated with better clinical outcomes. |
| Commentary  (Villar, 2010)28 | Commentary on Determann et al., study published in 2010. Villar felt that the study was stopped unnecessarily and early and was an unfortunate decision as questions regarding low tidal volume ventilation could have been answered. There was no strong safety signal, with virtually identical trends in terms of duration of mechanical ventilation and mortality rate in both groups. Early stopping tends to overestimate the results. |

## Annotated Bibliography

1. Klompas M, Branson R, Eichenwald EC, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014 Sep;35(Suppl 2):S133-54.PMID: 25376073.
2. Serpa Neto A, Simonis FD, Barbas CS, et al. Lung-protective ventilation with low tidal volumes and the occurrence of pulmonary complications in patients without acute respiratory distress syndrome: a systematic review and individual patient data analysis. Crit Care Med. 2015 Oct;43(10):2155-63. PMID: 26181219.

PRO: Retrospective cohort study. Conducted an individual patient data analysis to determine the relationship between tidal volume and the onset of pulmonary complications in ICU patients without ARDS. The study assigned patients into tidal volume groups based on the tertiles of tidal volume size the patient had received during the first 2 days of ventilation. Patients were assigned to a “low tidal volume group” (tidal volumes ≤7 mL/kg PBW), an “intermediate tidal volume group” (tidal volumes >7 mL/kg PBW and <10 mL/kg PBW), and a “high tidal volume group” (≥10 mL/kg PBW). This study included 2,184 patients. ARDS or pneumonia occurred in 23 percent of patients in the low tidal volume group, in 28 percent of patients in the intermediate tidal volume group, and in 31 percent of the patients in the high tidal volume group. Adjusted odds ratio (OR) [low tidal volume group vs. high tidal volume group] was 0.72; 95% CI, 0.52 to 0.98; with a significance (p) level of 0.042.; adjusted OR [intermediate group vs. high tidal volume group], 0.93; 95% confidence interval (CI), 0.69 to 1.24; with a significance (p) level of 0.635; R2, 0.034; Hosmer and Lemeshow p, 0.027. They concluded "ventilation with low tidal volumes is associated with a lower risk of development of pulmonary complications in patients without ARDS."

1. Fernandez-Bustamante A, Klawitter J, Repine JE, et al. Early effect of tidal volume on lung injury biomarkers in surgical patients with healthy lungs. Anesthesiology. 2014 Sep;121(3):469-81. PMID: 24809976.

CON: Prospective cohort study. RCT to observe the immediate tidal volume-related changes on lung injury biomarkers in patients with healthy lungs and low risk of pulmonary complications. No significant differences in biomarkers were detected between the Vt groups at any time. The coefficient of variation of exhaled breath condensate nitrite and nitrate decreased in the Vt 6 but increased in the Vt 10 group after 60 minutes of ventilation. Sixty-minute ventilation significantly increased plasma neutrophil elastase levels in the Vt 6 (35.2 ± 30.4 vs. 56.4 ± 51.7 ng/ml, p=0.008) and Clara Cell protein 16 levels in the Vt 10 group (16.4 ± 8.8 vs. 18.7 ± 9.5 ng/ml, p=0.015). Exhaled breath condensate nitrite correlated with plateau pressure (r=0.27, p=0.042) and plasma neutrophil elastase (r=0.44, p=0.001). Plasma Clara Cell protein 16 correlated with compliance (r=0.34, p=0.014). No significant tidal volume-related changes were found in the selected lung injury biomarkers of these patients (in the two Vt - 6 and 10 groups) with healthy lungs after 60 minutes of ventilation.

1. Futier E, Constantin JM, Paugam-Burtz C, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med. 2013 Aug 1;369(5):428-37. PMID: 23902482.

PRO: Multicenter, double-blind, parallel-group trial. Four hundred adults at risk of pulmonary complications after major abdominal surgery were randomly assigned to either nonprotective mechanical ventilation or a strategy of lung-protective ventilation. The two groups had similar characteristics at baseline. In an intention-to-treat analysis, the primary outcome, a composite of major pulmonary and extrapulmonary complications occurring within the first 7 days after surgery, occurred in 21 of 200 patients (10.5%) assigned to lung-protective ventilation, as compared with 55 of 200 (27.5%) assigned to nonprotective ventilation (relative risk, 0.40; 95% CI, 0.24 to 0.68; p=0.001). Over the 7-day postoperative period, 10 patients (5.0%) assigned to lung-protective ventilation required noninvasive ventilation or intubation for acute respiratory failure, as compared with 34 (17.0%) assigned to nonprotective ventilation (relative risk, 0.29; 95% CI, 0.14 to 0.61; p=0.001). The length of the hospital stay was shorter among patients receiving lung-protective ventilation than among those receiving nonprotective ventilation (mean difference, -2.45 days; 95% CI, -4.17 to -0.72; p=0.006).

1. Severgnini P, Selmo G, Lanza C, et al. Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. Anesthesiology. 2013 Jun;118(6):1307-21. PMID: 23542800.

PRO: Prospective RCT. Determined the effectiveness of protective mechanical ventilation during open abdominal surgery on a modified Clinical Pulmonary Infection Score (primary outcome) and postoperative pulmonary function. Randomly assigned 58 patients undergoing abdominal surgery lasting more than 2 hours to a standard ventilation strategy (tidal volume of 9 mL/kg ideal body weight and 0 PEEP) or to a protective ventilation strategy (tidal volume of 7 mL/kg ideal body weight, 10 cm H2O PEEP, and recruitment maneuvers). Patients ventilated with the protective strategy showed better pulmonary functional tests up to day 5, fewer alterations on chest x ray up to day 3 and higher arterial oxygenation in air at days 1, 3, and 5 (mmHg; mean ± standard deviation): 77.1 ± 13.0 versus 64.9 ± 11.3 (p=0.0006), 80.5 ± 10.1 versus 69.7 ± 9.3 (p=0.0002), and 82.1 ± 10.7 versus 78.5 ± 21.7 (p=0.44) respectively. The modified Clinical Pulmonary Infection Score was lower in the protective ventilation strategy at days 1 and 3. The percentage of patients in hospital at day 28 after surgery was not different between groups (7% vs. 15% respectively, p=0.42).

1. Lellouche F, Dionne S, Simard S, et al. High tidal volumes in mechanically ventilated patients increase organ dysfunction after cardiac surgery. Anesthesiology. 2012 May;116(5):1072-82. PMID: 22450472.

PRO: Prospective cohort study. Evaluated the impact of low, traditional, and high tidal volumes on cardiac surgery outcomes. They enrolled 3,434 consecutive adult patients. Three groups of patients were defined based on the tidal volume delivered on arrival at the intensive care unit:

* Low: below 10 mL/kg PBW
* Traditional: between 10­­ and 12 mL/kg PBW
* High: more than 12 mL/kg PBW

Risk factors were assessed for three types of organ failure (prolonged mechanical ventilation, hemodynamic instability, and renal failure) and a prolonged stay in the intensive care unit. Upon enrollment in the study, the mean tidal volume/actual weight was 9.2 mL/kg, and the tidal volume/PBW was 11.5 mL/kg. Low, traditional, and high tidal volumes were used in 724 (21.1%), 1,567 (45.6%), and 1,143 patients (33.3%), respectively. Independent risk factors for high tidal volumes were body mass index of 30 or more (OR 6.25; CI: 5.26-7.42; p<0.001) and female sex (OR 4.33; CI: 3.64 to 5.15; p<0.001). In the multivariate analysis, high and traditional tidal volumes were independent risk factors for organ failure, multiple organ failure, and prolonged stay in the intensive care unit. Organ failure was associated with increased intensive care unit stay, hospital mortality, and long-term mortality. Though it is important to note that the authors characterized "low" tidal volume at <10 mL/kg PBW (vs. 4–6 mL/kg), it is equally important to note that higher tidal volumes were associated with increased LOS and mortality.

1. Sundar S, Novack V, Jervis K, et al. Influence of low tidal volume ventilation on time to extubation in cardiac surgical patients. Anesthesiology. 2011 May;114(5):1102-10. PMID: 21430518.

PRO: Randomized clinical trial. Single-center trial with 149 patients undergoing elective cardiac surgery. Compared ventilation with 6 versus 10 mL/kg PBW tidal volume. Settings were applied immediately after anesthesia induction and continued throughout surgery and subsequent ICU stay. Primary endpoint was time to extubation. Secondary endpoints included the proportion of patients extubated at 6 hours and indices of lung mechanics and gas exchange, as well as clinical patient outcomes. Reduction in tidal volume did not significantly shorten time to extubation at 6 hours. However, there were other improvements. By 8 hours, 53.3 percent of patients in the low tidal volume group were free of an ventilation as compared to the control group at 31.1 percent (p=0.006).

1. Pinheiro de Oliveira R, Hetzel MP, dos Anjos Silva M, et al. Mechanical ventilation with high tidal volume induces inflammation in patients without lung disease. Crit Care. 2010 Mar;14(2):R39. PMID: 20236550.

PRO: Randomized clinical trial. Double-center trial with 20 patients without lung disease, requiring mechanical ventilation admitted to either a trauma or a general intensive care unit of two different university hospitals. Patients were randomized to receive mechanical ventilation with either tidal volume of 10 to 12 mL/kg PBW (high Vt group) or 5 to 7 mL/kg PBW (low Vt group), with an FiO2 high enough to keep arterial oxygen saturation >90 percent and a PEEP of 5 cm H2O. TNF-alpha and IL-8 concentrations were measured in the serum and in the BAL fluid at admission and after 12 hours of study observation time. There were no differences in TNF-alpha or IL-8 concentrations at 12 hours at first analysis. However, standardization against urea of logarithmic transformed data revealed that TNF-alpha and IL-8 level in BAL fluid were stable in the low Vt group, but increased in the high Vt group (p=0.05 and p=0.03).

1. Determann RM, Royakkers A, Wolthuis EK, et al. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. Crit Care. 2010 Jan;14(1):R1. PMID: 20055989.

PRO: Randomized clinical trial. This study compared mechanical ventilation with tidal volumes of 10 mL/kg versus 6 mL/kg PBW in critically ill patients without ALI. The trial was halted for safety reasons when they observed that the development of lung injury was higher in the conventional tidal-volume group as compared with the lower tidal-volume group (13.5% versus 2.6%; p=0.01). One hundred fifty patients (74 conventional vs. 76 lower tidal volume) were enrolled and analyzed. No differences were observed in lavage fluid cytokine levels at baseline between the randomization groups. Plasma interleukin-6 (IL-6) levels decreased significantly more strongly in the lower-tidal-volume group (from 51 [20 to 182] ng/mL to 11 [5 to 20] ng/mL vs. 50 [21 to 122] ng/mL to 21 [20 to 77] ng/mL; p=0.01). Univariate analysis showed statistical relations between baseline lung-injury score, randomization group, level of PEEP, the number of transfused blood products, the presence of a risk factor for ALI, and baseline IL-6 lavage fluid levels and the development of lung injury. Multivariate analysis revealed the randomization group and the level of PEEP as independent predictors of the development of lung injury. Thus, conventional tidal volumes contributed to the development of lung injury in patients without ALI at the onset of mechanical ventilation.

1. Mascia L, Zavala E, Bosma K, et al. High tidal volume is associated with the development of acute lung injury after severe brain injury: An international observational study. Crit Care Med. 2007 Aug;35(8):1815-20. PMID: 17568331.

PRO: Prospective, multicenter, observational study in 4 European ICUs in academic medical centers, with 86 severely brain-injured patients enrolled in 13 months. Patients were studied for 8 days post admission. Eighteen patients (22%) developed ALI on day 2.8 ±1. They were initially ventilated with significantly higher Vt per PBW (9.5 +/- 1 vs 10.4 +/- 1.1, respiratory rate, and minute ventilation and more often required vasoactive drugs (p<.05) In addition to a lower Pao2/Fio2 (OR 0.98, 95% CI 0.98 to 0.99), the use of high Vt (OR 5.4, 95% CI 1.54 to 19.24) and relatively high respiratory rate (OR 1.8, 95% CI 1.13 to 2.86) were independent predictors of ALI (p<0.01). After onset of ALI, patients remained ventilated with similar Vt to maintain mild hypocapnia and had a longer length of stay in the ICU and fewer ventilator-free days. In this patient population, alternative ventilator strategies should be considered to protect the lung and guarantee a tight carbon dioxide (CO2) control.

1. Choi G, Wolthuis EK, Bresser P, et al. Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents alveolar coagulation in patients without lung injury. Anesthesiology. 2006 Oct;105(4):689-95. PMID: 17006066.

PRO: Randomized clinical trial. Patients scheduled for an elective surgical procedure (lasting ≥5 hours) were randomized to mechanical ventilation with either higher Vt of 12 mL/kg ideal body weight and no PEEP (n=21) or lower Vt of 6 mL/kg ideal body weight and 10 cm H2O PEEP. After induction of anesthesia and 5 hours later, BAL fluid and blood samples were obtained, and markers of coagulation and fibrinolysis were measured. Mechanical ventilation with higher Vt without PEEP was associated with an increase in soluble thrombomodulin in lavage fluids and lower levels of bronchoalveolar activated protein C in comparison with lower Vt volumes and PEEP. Bronchoalveolar fibrinolytic activity did not change by either ventilation strategy. Mechanical ventilation with higher Vt and no PEEP promotes procoagulant changes, which are largely prevented by the use of lower Vt and PEEP.

1. Gajic O, Frutos-Vivar F, Esteban A, et al. Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. Intensive Care Med. 2005 Jul;31(7):922-6. PMID: 15856172.

PRO: Retrospective cohort study. Identified patients who required mechanical ventilation for at least 48 hours, but did not have ARDS at the onset of mechanical ventilation. Information was collected from a large international mechanical ventilation study database. Primary outcome was development of ARDS after the onset of mechanical ventilation. A total of 3,261 patients met criteria, and 205 patients (6.2%) developed ARDS ≥48 hours after the onset of mechanical ventilation. Multivariate logistic regression analysis adjusted for baseline characteristics and underlying ARDS risk factors (sepsis, trauma, pneumonia) found the development of ARDS to be associated with the initial ventilator settings: high Vt (OR 2.6 for Vt >700 mL), high peak airway pressure (OR 1.6 for peak airway pressure >30 cm H2O), and high PEEP (OR 1.7 for PEEP >5 cm H2O). The association with the potentially injurious initial ventilator settings, in particular large Vt, suggests that ARDS in mechanically ventilated patients is in part a preventable complication.

1. Schilling T, Kozian A, Huth C, et al. The pulmonary immune effects of mechanical ventilation in patients undergoing thoracic surgery. Anesth Analg. 2005 Oct;101(4):957-65. PMID: 16192502.

PRO: Randomized clinical trial. Patients undergoing open thoracic surgery (n=32) were randomized to receive mechanical ventilation with either Vt=10 mL/kg (n=16) or Vt=5 mL/kg (n=16) adjusted to normal Pa(CO2) during and after one-lung ventilation. BAL fluid test of ventilated lung was performed, and cells, protein, tumor necrosis factor (TNF)-alpha, interleukin (IL)-8, soluble intercellular adhesion molecule (slCAM)-1, IL-10, and elastase were determined in the BAL. Data were analyzed by parametric or nonparametric tests, as indicated. In all patients, an increase of proinflammatory variables was found. The time courses of intra-alveolar cells, protein, albumin, IL-8, elastase, and IL-10 did not differ between the groups after one-lung ventilation and postoperatively. TNF-alpha (8.4 vs. 5.0 microg/mL) and slCAM (52.7 vs. 27.5 microg/mL) concentrations were significantly smaller after one-lung ventilation with Vt=5 mL/kg. These results indicate that mechanical ventilation may reduce alveolar concentrations of TNF-alpha and of slCAM-1; Reductions of Vt, with subsequently decreased peak airway pressures, may reduce some alveolar inflammatory responses seen with mechanical ventilation.

1. Gajic O, Dara SI, Mendez JL, et al. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. Crit Care Med. 2004;32(9):1817-24. PMID: 15343007.

PRO: Retrospective cohort study. Patients who received invasive mechanical ventilation for ≥ 48 hours in four ICUs in a tertiary referral center between January and December 2001. ALI, the main outcome, was assessed by independent review of daily digital chest radiographs and arterial blood gases. A total of 332 patients did not have ALI from the outset, though 80 patients (24%) developed ALI within 5 days of mechanical ventilation. Per PBW, women were ventilated with a higher Vt than men (mean 11.4 vs. 10.4 mL/kg PBW, p<0.001) and tended to develop ALI more often (29% vs. 20%, p=0.068). In a multivariate analysis, the main risk factors associated with the development of ALI were the use of large Vt (OR, 1.3 for each mL above 6 mL/kg PBW, p<0.001), transfusion of blood products (OR, 3.0; p<0.001), acidemia (pH <7.35; OR, 2.0; p=0.032), and a history of restrictive lung disease (OR, 3.6; p=0.044). The association between initial Vt and the development of ALI suggests that ventilator-associated lung injury may be an important cause of this syndrome. Height and gender should be considered when setting up the ventilator. Strong consideration should be given to limiting large Vt, not only in patients with established ALI, but also in patients at risk for ALI.

1. Koner O, Celebi S, Balci H, et al. Effects of protective and conventional mechanical ventilation on pulmonary function and systemic cytokine release after cardiopulmonary bypass. Intensive Care Med. 2004 Sep;30(4):620-6. PMID: 14722635.

CON: Randomized clinical trial. Patients (n=44) undergoing elective coronary bypass grafting surgery with cardiopulmonary bypass from a single university hospital were enrolled. Patients were ventilated with—

1. Protective Vt (PV) (6 mL/kg, respiratory rate: 15 breaths per min, PEEP 5 cm H2O, n=15) group PV
2. Conventional Vt (CV) (10 mL/kg, respiratory rate: 9 breaths per min, PEEP 5 cm H2O, n=14)
3. Group CV+ZEEP (Zero PEEP)

Pulmonary parameters, including systemic TNF-alpha and IL-6 levels were determined throughout the study. There were no differences among the groups regarding the systemic TNF-alpha and IL-6 levels. The plateau airway pressures of group PV were lower than those groups of CV+PEEP (p=0.02) and CV+ZEEP (p=0.001) after cardiopulmonary bypass. The shunt fraction of group PV was significantly lower than that of group CV+ZEEP 24 hours after surgery (<0.05). Oxygenation and the alveolar-arterial oxygen differences were better in both PEEP groups than in group CV+ZEEP 24 hours after surgery. There was no evidence that protective mechanical ventilation prevents some of the adverse effects of cardiopulmonary bypass on the lung, nor systemic cytokine levels, postoperative pulmonary function or length of hospitalization.

1. Wrigge H, Uhlig U, Zinserling J, et al. The effects of different ventilatory settings on pulmonary and systemic inflammatory responses during major surgery. Anesth Analg. 2004 Mar;98(3):775-81. PMID: 14980936.

CON: Randomized clinical trial. Total of 64 patients undergoing elective thoracotomy (n=34) or laparotomy (n=30) were randomized to receive either mechanical ventilation with Vt=12 or 15 mL/kg ideal body weight, respectively, and ZEEP, or Vt=6 mg/kg ideal body weight with positive PEEP of 10 cm H2O. In 63 patients who completed the study, there was no difference in arterial oxygenation between the groups. TNF-alpha, IL-1, IL-6, IL-8a and IL-12 were all determined by cytometric bead array in plasma after 0, 1, 2, and 3 hours and in tracheal aspirates after 3 hours of mechanical ventilation. Data were log-transformed and analyzed using parametric or nonparametric tests as indicated. All plasma mediators increased more during abdominal than during thoracic surgery, although the differences were small. However, neither time course nor concentrations of pulmonary or systemic mediators differed between the two ventilatory settings. These data suggest that the ventilatory settings studied do not affect inflammatory reactions during major surgery within 3 hours.

1. Chaney MA, Nikolov MP, Blakeman BP, et al. Protective ventilation attenuates postoperative pulmonary dysfunction in patients undergoing cardiopulmonary bypass. J Cardiothorac Vasc Anesth. 2000 Oct;14(5):514-8. PMID: 11052430.

PRO: Randomized clinical trial. Patients (n=25) undergoing elective coronary bypass graft procedure and early extubation from a single university hospital were enrolled. Thirteen patients received conventional mechanical ventilation (CV; respiratory rate, 8 breaths per min; Vt, 12 mL/kg; FiO2, 1.0; PEEP, +5), and 12 patients received protective mechanical ventilation (PV; respiratory rate, 16 breaths per min; Vt, 6 mL/kg; FiO2, 1.0; PEEP, +5). Perioperative anesthetic and surgical management were standardized. Various pulmonary parameters were determined at 10 minutes after intubation and 60 minutes after arrival in the ICU. The mean postoperative increase in peak airway pressure was significantly larger in group PV (7.1 vs. 2.4 cm H2O; p<0.001). Group CV experienced significant postoperative increases in plateau pressure (p=0.007), but group PV did not (p=0.644). The mean postoperative decrease in dynamic lung compliance in group CV was significantly larger than that in group PV (14.9 vs. 5.5 mL/cm H2O; p=0.002). Group CV experienced significant postoperative decreases in static lung compliance (p=0.014), but group PV did not (p=0.645). Group CV experienced significant postoperative increases in shunt (15.5% to 21.4%; p=0.021), but group PV did not (18.4% to 21.2%; p=0.265). Protective ventilation decreased lung damage caused by mechanical ventilation in normal and abnormal lungs. Protective ventilation may also help attenuate the postoperative pulmonary dysfunction (increases in airway pressure, decreases in lung compliance, and increases in shunt) commonly seen in patients after exposure to coronary bypass.

1. Lee PC, Helsmoortel CM, Cohn SM, et al. Are low tidal volumes safe? Chest. 1990 Feb;97(2):430-4. PMID: 2288551.

Neither PRO nor CON: Randomized clinical trial. Intubated patients in the SICU were randomly assigned to group 1 (Vt=12 mg/mL, n=56) or group 2 (Vt=6 mL/kg, n=47). Collected variables included Acute Physiology and Chronic Health Evaluation II (APACHE II) score, mean peak airway pressure, mean PaO2/FiO2, incidence of pulmonary infectious complications, duration of intubation, and duration of SICU stay. Incidence of pulmonary infection tended to be lower, and duration of intubation and duration of SICU stay tended to be shorter for non-neurological and noncardiac surgical patients randomized to low Vt, suggesting morbidity may be decreased, though findings were not statistically significant. The use of low Vt was associated with a statistically significant but clinically irrelevant decrease in oxygenation. The routine use of low Vt appeared to be safe in a selected population of patients in the ICU.

1. Pannu SR, Hubmayr RD. Safe mechanical ventilation in patients without acute respiratory distress syndrome (ARDS). Minerva Anestesiol. 2015 Sep;81(9):1031-40. PMID: 25598293.

Review. Reviewed studies in the medical and surgical literature that have addressed "lung-protective ventilation" in patients without ARDS specifically with a focus on the associations with tidal volume, PEEP, and oxygen supplementation settings. Citing that the incidence of ARDS acquired after mechanical ventilation is 6–25 percent, from their review, they also concluded that tidal volumes between 6 and 8 mL/kg PBW are safe and typically meet gas exchange targets in the vast majority of patients without ARDS.

1. Sutherasan Y, Vargas M, Pelosi P. Protective mechanical ventilation in the noninjured lung: review and meta-analysis. Crit Care. 2014 Mar 18;18(2):211. PMID: 24762100.

Review of current literature and most current meta-analyses, plus a separate meta-analysis focusing on RCTs in patients undergoing surgery and critically ill patients, and excluding one-lung ventilation. Seventeen articles were included in the meta-analysis, including 1,362 patients. Protective ventilation was given to 682 patients, and 680 patients had conventional ventilation. The average Vt for the protective and conventional ventilation were 6.1 mL/kg ideal body weight and 10.7 mL/kg, respectively. The protective ventilation group had a lower incidence of acute lung injury (RR 0.27, 95% CI 0.12 to 0.59) and lung infection (RR 0.35, 95% CI 0.25 to 0.63). Application of protective ventilation did not have an effect on atelectasis (RR 0.76, 95% CI 0.33 to 1.37) or mortality (RR 1.03, 95% CI 0.67 to 1.58). There were no differences in length of ICU stay weighted mean difference (WMD) -0.40, 95% CI 0.22 to 1.02 or length of hospital stay (WMD 0.13, 95% CI 0.08 to 0.73). This study showed that among surgical and critically ill patients without lung injury, protective mechanical ventilation is associated with better clinical pulmonary outcomes in terms of ARDS incidence and pulmonary infection, but does not decrease atelectasis, mortality, or length of stay.

1. Futier E, Godet T, Millot A, et al. Mechanical ventilation in abdominal surgery. Ann Fr Anesth Reanim. 2014 Jul-Aug;33(7-8):472-5. PMID: 25153670.

Clinical review. Reviewed clinical evidence regarding the use of mechanical ventilation in patients undergoing abdominal surgery. Concluded that the use of a prophylactic multifaceted strategy of mechanical ventilation, composed of low tidal volume ventilation, moderate PEEP, and repeated recruitment maneuvers, can help improve postoperative outcome after abdominal surgery.

1. Coppola S, Froio S, Chiumello D. Protective lung ventilation during general anesthesia: is there any evidence? Crit Care. 2014 Mar 18;18(2):210. PMID: 25029254.

Review. Reviewed evidence regarding the use of lung-protective mechanical ventilation. Concluded that strategy should be used for patients who will have prolonged anesthesia, in high-risk patients, or for high-risk surgery. They note that while the strategy of lung-protective ventilation is protective for the lungs, it may impair the cardiovascular system, reducing venous return and cardiac output and requiring the use of fluids and vasopressors. Therefore, the risks and benefits should be balanced for each patient.

1. Kilickaya O, Gajic O. Initial ventilator settings for critically ill patients. Crit Care. 2013 Mar;17(2):123. PMID: 23510269.

Commentary and review. Summarized the results of an observational data study, small randomized studies, and two systematic reviews that suggest that lung-protective ventilation is safe and potentially beneficial in patients without ARDS at the onset of mechanical ventilation. Their principles of lung-protective ventilation are listed here:

* 1. Prevention of volutrauma (tidal volume 4 to 8 mL/kg PBW with plateau pressure <30 cm H2O)
  2. Prevention of atelectasis (positive end-expiratory pressure ≥5 cm H2O, as needed recruitment maneuvers)
  3. Adequate ventilation (respiratory rate 20 to 35 breaths per min)
  4. Prevention of hyperoxia (titrate inspired oxygen concentration to peripheral oxygen saturation (SpO2) levels of 88 to 95%)

They highlighted that most patients tolerate lung-protective mechanical ventilation well without the need for excessive sedation and that patients with a stiff chest wall may tolerate higher plateau pressure targets (approximately 35 cm H2O) while those with severe ARDS and ventilator asynchrony may require a short-term neuromuscular blockade. Recommend that lung-protective mechanical ventilation is an initial approach to mechanical ventilation in both perioperative and critical care settings.

1. Fuller BM, Mohr NM, Drewry AM, et al. Lower tidal volume at initiation of mechanical ventilation may reduce progression to acute respiratory distress syndrome: a systematic review. Crit Care. 2013 Jan 18;17(1):R11. PMID: 23331507.

Systematic review. Systematic literature searches of MEDLINE, EMBASE, CINAHL, the Cochrane Library, conference proceedings, and clinical trial registration were performed with a comprehensive strategy. Included studies provided information on mechanically ventilated patients without ARDS at the time of initiation of mechanical ventilation, and in which tidal volume was independently studied as a predictor variable for outcome. The primary outcome was progression to ARDS. The search yielded 1,704 studies, of which 13 were included in the final analysis. One randomized controlled trial was found; the remaining 12 studies were observational. The patient cohorts were significantly heterogeneous in composition and baseline risk for developing ARDS; therefore, a meta-analysis of the data was not performed. The majority of the studies (n=8) showed a decrease in progression to ARDS with a lower tidal volume strategy.

1. Lellouche F, Lipes J. Prophylactic protective ventilation: lower tidal volumes for all critically

ill patients? Intensive Care Med. 2013 Jan;39(1):6-15. PMID: 23108608.

Review. Conducted a literature review to examine the use of prophylactic protective ventilation (i.e., LTVV) in patients without ARDS. Recommends the use of a Vt of 6—8 ml/kg PBW in patients with risk factors for the development of lung injury, such as multiple transfusions, trauma, sepsis, or high-risk surgery. Considering the proven rationale and current evidence, this prophylactic protective ventilation strategy can be recommended for almost all mechanically ventilated patients who do not yet have ARDS. The use of a ventilation strategy that incorporates tidal volume reduction based on PBW and moderately high PEEP in the majority of ICU intubated patients and at initiation of invasive mechanical ventilation is reasonable.

1. Biehl M, Kashiouris MG, Gajic O. Ventilator-induced lung injury: minimizing its impact in patients with or at risk for ARDS. Respir Care. 2013 Jun;58(6):927-37. PMID: 23709192.

Review. Conducted a review to highlight the best VILI preventive approach in patients with or at risk for ARDS and to critically appraise evidence and expert opinion. Existing evidence favors the practice of Vt and that the use of protective Vt ventilation is "safe and effective in maintaining gas exchange in patients without ARDS [while in] mechanically ventilated patients at risk of ARDS, exposure to high Vt increases the frequency of ARDS."

1. Neto AS, Cardoso SO, Manetta JA, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. JAMA. 2012 Oct 24;308(16):1651-9. PMID: 23093163.

Review. Reviewed the best VILI preventive approach in patients with or at risk for ARDS and critically appraised evidence and expert opinions. Authors asserted that existing evidence favors the practice of Vt and that the use of protective Vt ventilation is "safe and effective in maintaining gas exchange in patients without ARDS [while in] mechanically ventilated patients at risk of ARDS, exposure to high Vt increases the frequency of ARDS."

1. Villar J, Slutsky AS. Is acute respiratory distress syndrome an iatrogenic disease? Crit Care. 2010 Feb;14(1):120. PMID: 20236490.

Commentary. Response to Determann et al. randomized clinical trial (citation #20) halted due to safety reasons (concerns about increased development of lung injury in the conventional arm). Villar felt that the study was stopped unnecessarily and early and was an unfortunate decision as questions regarding low tidal volume ventilation could have been answered. There was no strong safety signal, with virtually identical trends in terms of duration of mechanical ventilation and mortality rate in both groups. Early stopping tends to overestimate the results.

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